COMBINED GRAND ROUNDS

DEPARTMENT OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY

NATIONAL NAVAL MEDICAL CENTER

WALTER REED ARMY MEDICAL CENTER

PARAGANGLIOMA OF THE HEAD AND NECK

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OCTOBER 5TH, 2000

Overview

- Introduction
- Historical Background and Terminology
- Anatomy and physiology
- Classification and Subtypes
- Work-up and Management
- Summary and Conclusions

Introduction

- Paragangliomas are benign tumors that arise from branchiomeric paraganglia distributed along the course of autonomic nerves from skull base to aortic arch
- Called nonchromaffin paragangliomas because they lack positive response to chromaffin staining associated with Neural crest tumors of adrenal gland
- Derived from Neural crest cells
- Typically occur along course of major vasculature and autonomic nerves
- Generally are benign, slow growing tumors

Introduction

- All paragangliomas are related to one another, and to pheochromocytomas of the adrenal gland
- In contrast to Pheochromocytomas, they rarely secrete catecholamines
- Consist of Type I or chief cells which are members of the amine precursor and uptake decarboxylase (APUD) family
- Type II cells are sustentacular cells
- Nuclear polymorphism and cellular hyperchromatism common : not considered evidence of malignancy
- Can also be found in the orbit, larynx, paranasal sinuses and oral cavity

Historical background and terminology

- Carotid body first described by anatomist Von Haller in 1743
- Renamed carotid gland after histologic identification of glandular acini
- Renamed vascular glomerulus or glomus in early 20th century
- Paraganglion first used by histologist Kohn while describing carotid body
- 1941, Guild described “glomic tissue” for vascularized tissue on promontory and jugular bulb

Historical background and terminology

- 1945, Rosenwasser reported a “carotid body tumor” of middle ear and mastoid
- Glenner and Grimmley distingushed adrenal (pheochromocytomas) and extra-adrenal paraganglionma
- Other terms like Chemodectomas and nonchromaffin tumors used
- CURRENTLY, PARAGANGLIOMA BASED ON ANATOMIC LOCATION IS PROPER TERMINOLOGY (e.g. carotid paraganglioma, jugulotympanic paraganglioma)

Background and Terminology

- Carotid body tumor (carotid paraganglioma, chemodectoma)
- Intravagal Paragangliomas
- Jugulotympanic Paragangliomas
  - Glomus tympanicum
  - Glomus jugulare

Anatomy and Physiology

- Carotid Body and Sinus
- Jugular Foramen/ temporal bone

Carotid Sinus

- Composed of Stretch receptors which lie in the adventitia of carotid bulb
- First described by Heath in 1850
- Further identified by Manson in 1862 from his study of post-mortem exam of inmates
- Described areas of thinning of wall of carotid sinus area with absence of muscle fibers in the tunica media, but plentiful stretch fibers, receptors and nerve endings
- Innervation by afferent fibers from carotid body (1-2cm from bifurcation) to form Carotid sinus nerve

Carotid sinus

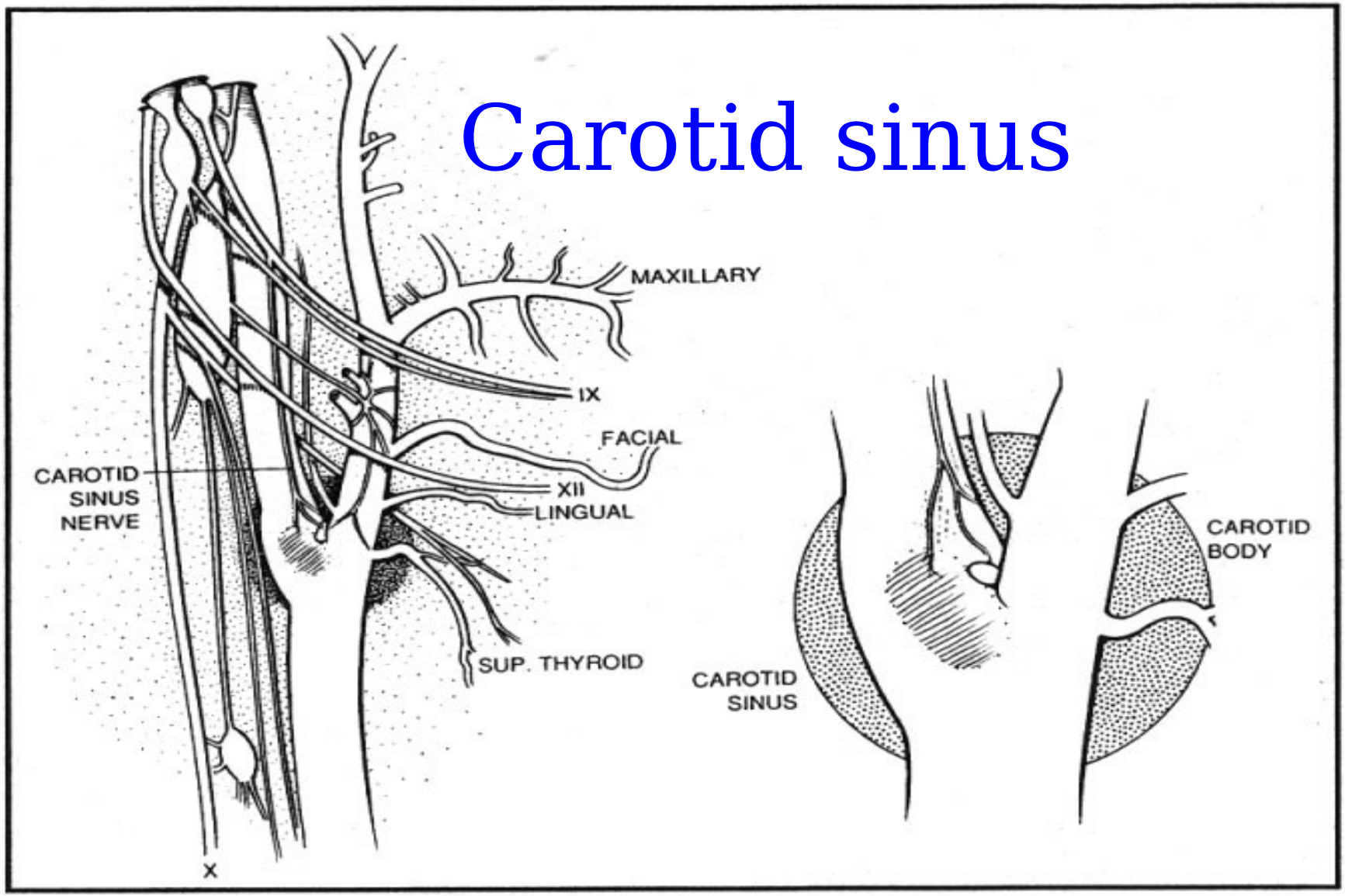


Fig. 1. The anatomy of the carotid sinus nerve as it divides into the branches to the carotid body and the carotid sinus is seen on the left. The enlargement on the right shows the relationship of the carotid body to the sinus.

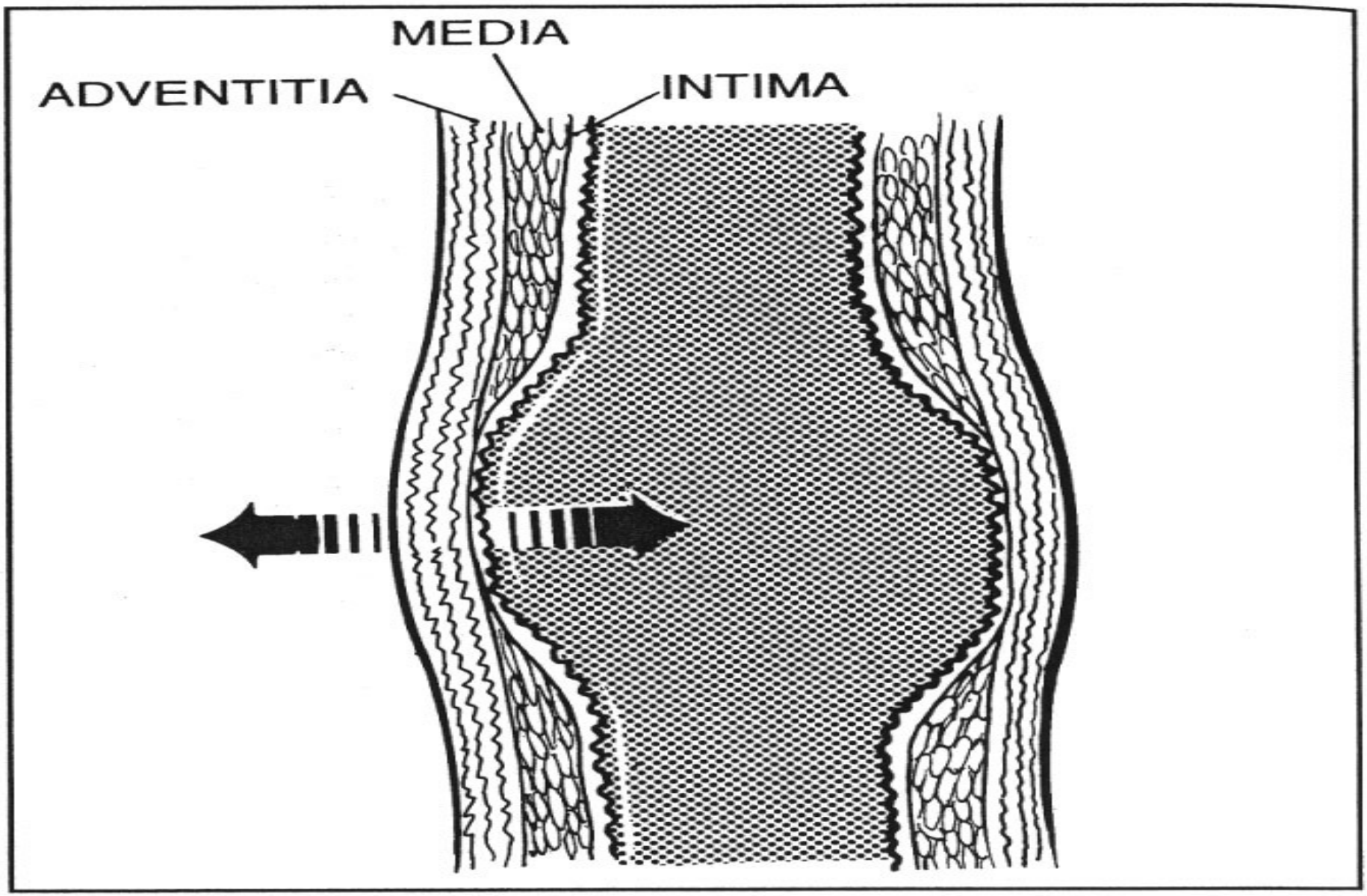


Fig. 2. The muscularis layer of the carotid is very thin in the region of the carotid sinus. This allows the elastic fibers of the sinus to be adjacent to the media layer of the carotid. The contact between these layers increases the sensitivity of the baroreceptor function.

Carotid Body

- One of Nonchromaffin paraganglia
- Associated with Parasympathetic nerves
- Composed of clusters of epithelium-like cells in a richly vascular connective tissue stroma numbering 20
- Divided into smaller units or Zellballen which are comprised of 2 receptor cell types namely Chief Cells (type 1, epithelioid , which contain catecholamine-bound neurosecretory granules) and Type 2 sustentacular cells(supporting cells)
- Bilateral location constant

Carotid Body

- Connected to carotid bifurcation by ligament of Mayer
- Blood supply from 1-2mm artery arising from bifurcation
- Average size 5 x 3 x 1.5mm
- Size increases with age and associated with high altitude dwellers
- Average wt = 12.1 mg, range 1.0 – 47.4mg
- Supplied by the Nerve of Hering, which is a branch of the glossopharyngeal nerve (Proven by DeCastro's sectioning of CN IX, then observing neural degeneration).
- Minor input from CN X and sympathetic trunk

Carotid Body/Sinus Physiology

- Function as chemoreceptor and baroreceptor complex
- Chemoreceptor mediated by carotid body, sensitive to changes in PaO_2, $PaCO_2$, pH and blood flow
- Daly, et al demonstrated blood flow to this tissue to be 4x thyroid and 3x brain, thus very vascular
- Constant output from CB participating in ventilation: Lower PaO_2 leads to increase in firing within carotid sinus nerve affecting increase ventilation.
- Higher $PaCO_2$ or lower pH also increase ventilation

Carotid Body/Sinus Physiology

- Baroreceptor effect mediated through carotid sinus, transmitted by nerve of hering, through CN IX, to tractus solitarius
- Carotid sinus made of type I and type II barorecptors which together temper extreme variations in blood pressure
- Resultant parasympathetic response leads to vasodilation and decreased heart rate and contractility in response to increased stimulation of baroreceptors
- Decrease baroreceptor activity decreases parasympathetic depression of heart and peripheral vasculature

Carotid Body Tumor

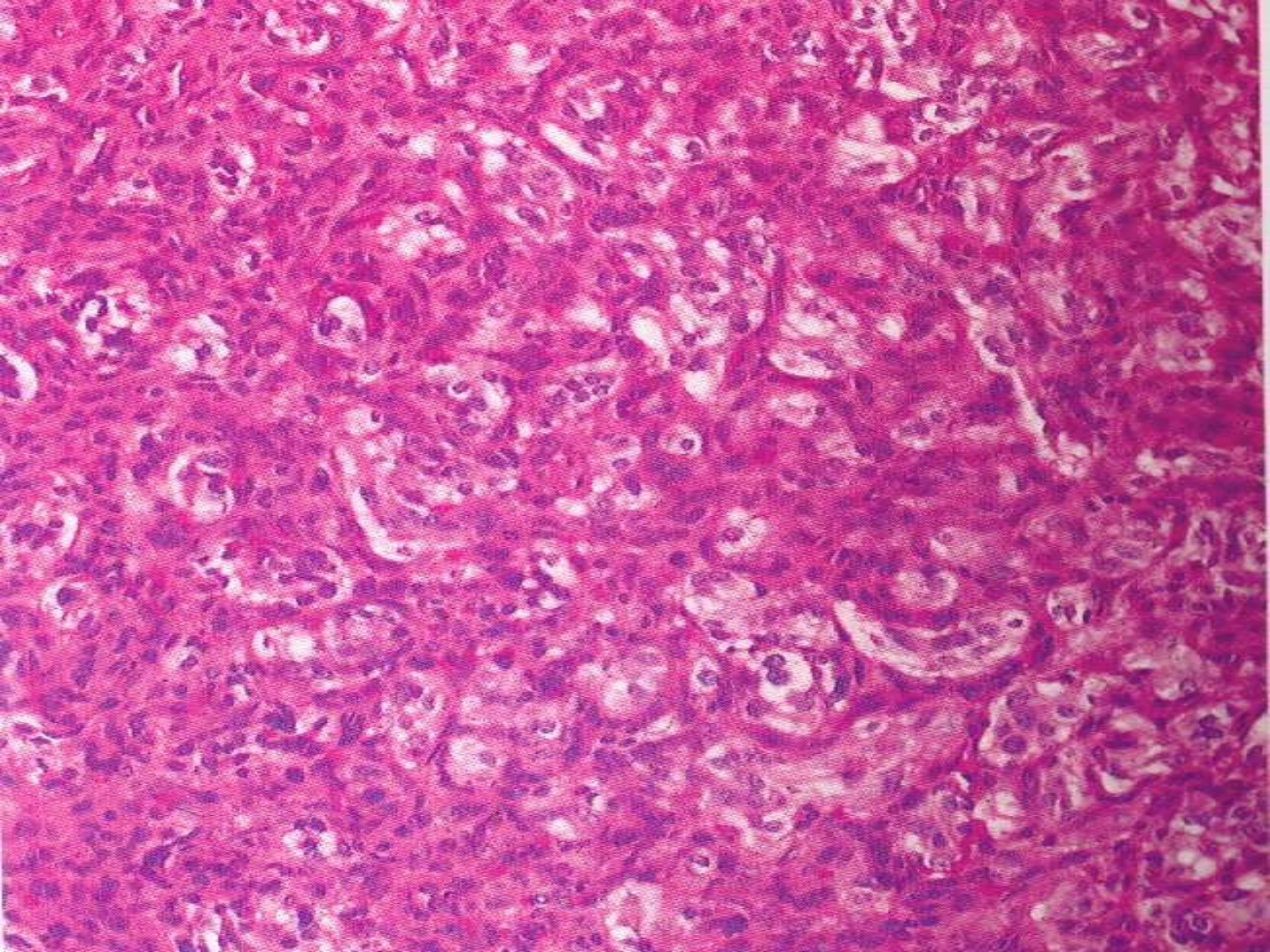
- Most common paraganglioma of head and neck comprising 60% of total
- Thought to be more common in people living in high altitudes
- Commonly occur in 5th decade
- Higher incidence in females
- Typically present as a slow growing painless neck mass, which is mobile antero-posteriorly, but immobile cranio-caudally
- May bulge through parapharyngeal area into OC/OP

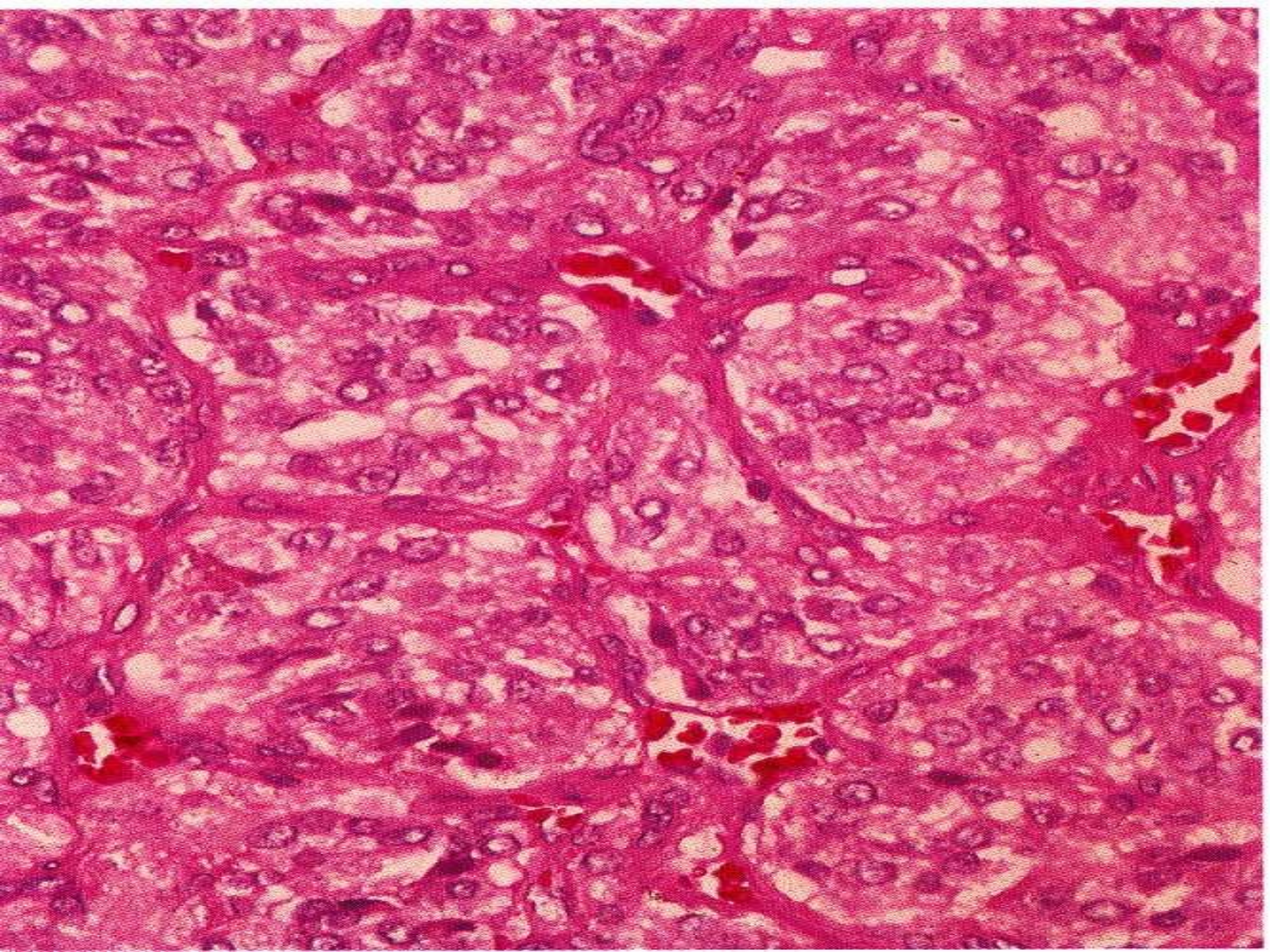
Carotid Body Tumor

- May present with hoarseness, VC paralysis, dysphagia, local discomfort, Headaches , blurred vision
- 10% are multicentric
- 20% are familial with a tendency for multicentricity in 50% of the familial cases
- Inheritance is AD (Mendelian) modified by genomic imprinting meaning that tumor develops (expression) when gene is paternally inherited and not when maternally inherited
- 8 – 10% are malignant, more common in familial variant

Carotid Body Tumor

- No histologic criteria for malignancy: malignancy diagnosed by evidence of spread to regional lymph nodes or distant sites (lung, bone, liver, pancreas, thyroid, kidney, breast)
- Pathophysiology related to mass and pressure effect of tumor on carotid body/sinus
- Can cause symptoms by physically expanding and compressing surrounding structures, especially nerves, and can be lethal if untreated
- Typically supplied by ascending pharyngeal artery



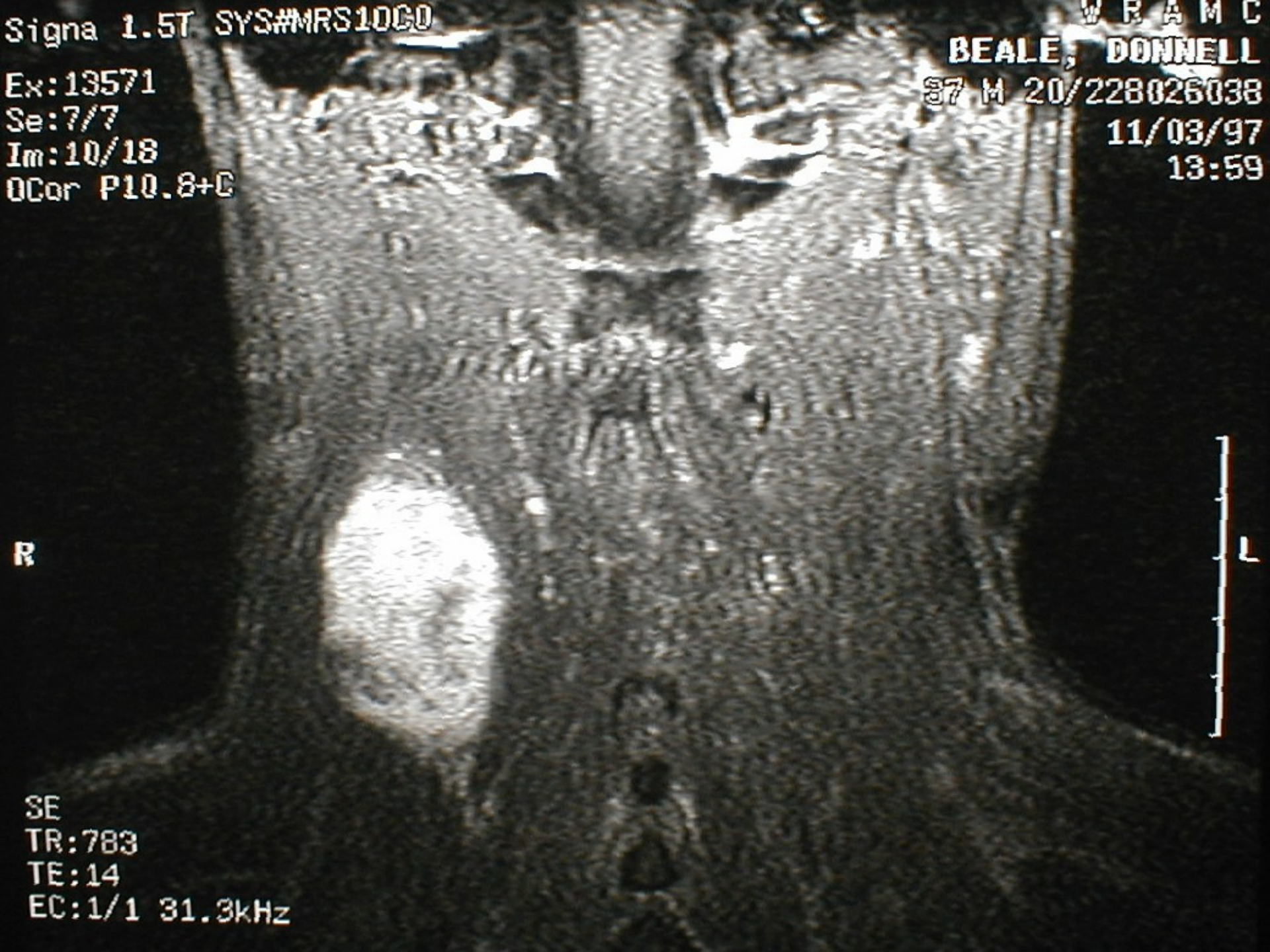


Carotid Body Tumor (DDX)

- Brachial cleft cyst, harmatoma
- Lymph node, SCCA
- Salivary gland tumor
- Neurofibroma, neuroblastoma, ganglion intercortium
- Carotid anourysm
- Plasmacytoma
- Hemangiopericytoma, myoblastoma,
- Angioendolethioma, chromaffinoma, endothelioma
- Angioma, Angiosarcoma, carcinoid, carcinoma, sarcoma

Carotid Body Tumor (work-up)

- FNA not advised as excessive bleeding will occur. Typically non-diagnostic due to excess blood in specimen
- MRI, CT with contrast and angiogram mainstay
- Typical Lyre sign and tumor blush seen on angio
- Angiogram also used to evaluate adequacy of carotid system
- Balloon test occlusion performed to evaluate circle of willis
- Urine VMA, catecholamines , metanephrines
- Abdominal CT if symptoms of catecholamines or positive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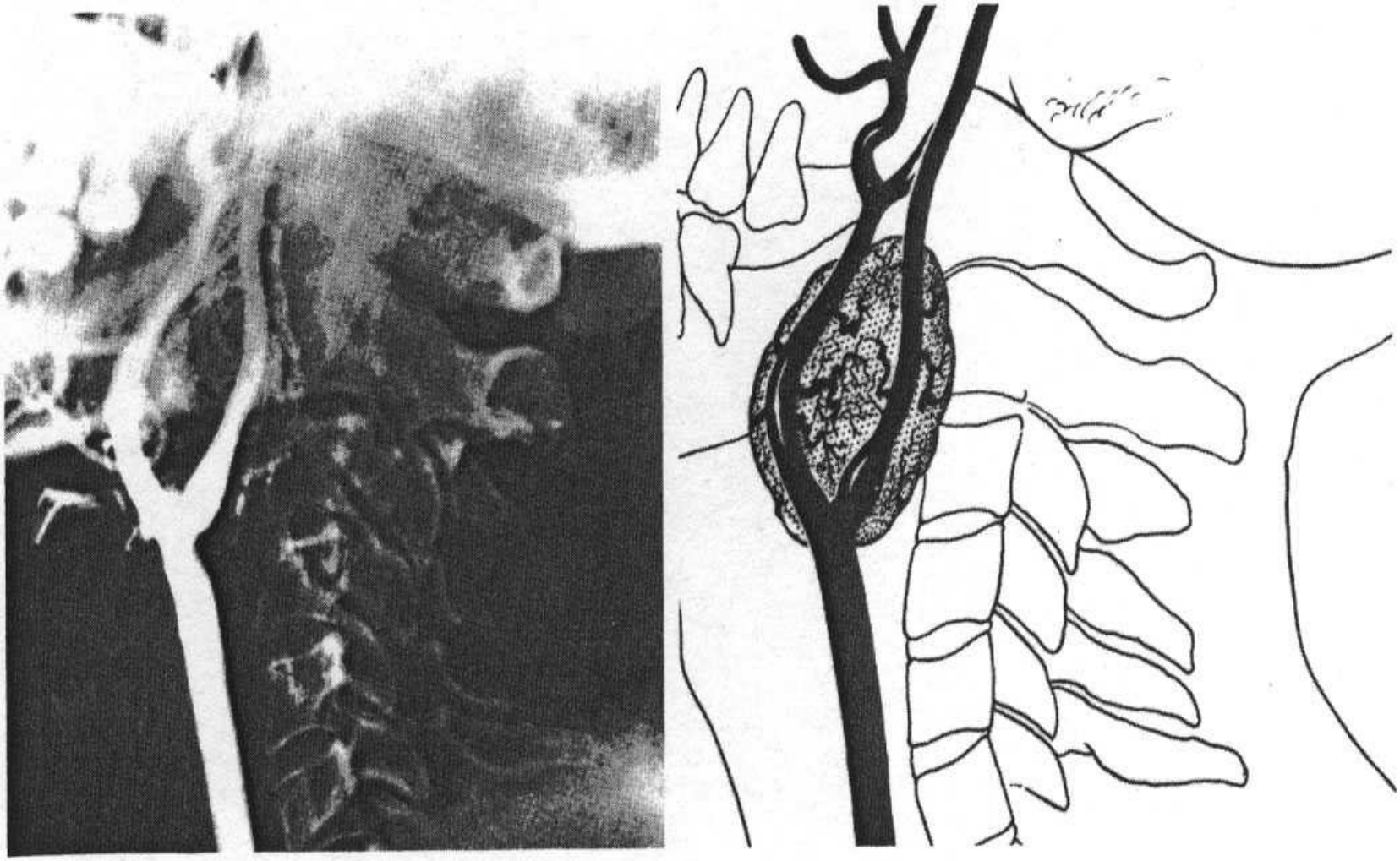


Figure 2. Left carotid angiogram in a 39 year old man with a carotid body paraganglioma. The drawing on the right depicts separation of the external and internal branches of the common carotid artery in the area of its bifurcation. The tumor measured 3 cm. in diameter.

Carotid Body Tumor (work-up)

- If familial, must evaluate for MEN syndromes
- If familial, risk individuals older than 16-18 yrs should be examined and screened with MRI every 2 years
- Octreotide scanning has been used for multicentric tumors or to screen family members
- Genetic screening emerging as a method of evaluation (chromosome 11q13 and q23)

Carotid body tumor (management)

- Surgery is mainstay for management
- If excised, may recur in 10% of cases
- Generally regarded as radio-resistant, XRT reserved for incompletely excised tumors (with intracranial extension), very large tumors, elderly patient, poor surgical candidates, or multicentricity
- Embolization typically performed 24 – 48 hrs prior to surgery. Questionable as to whether this decreases intraoperative bleeding. May also set up inflammatory response which makes surgery more difficult

Carotid body tumor (management)

- Overall operative mortality of 2-8%, stroke rate of 20%, CN X and XII damage rate of 40-50%
- Shamblin classification of operative morbidity based on tumor size
  - Group I tumors small and easy to remove
  - Group II tumors medium size , with attachment to carotid
  - Group III large with transmural invasion of carotid requiring resection and grafting

Carotid body tumor (management)

- McCaffrey found that carotid paragangliomas measuring greater than 5cm had operative complication rate of 67% compared to 14% if less than 5cm
- Post-operative denervation with sympathetic discharge can lead to high and fluctuating BP
- Managed with nitroprusside initially, then Clonidine (central alpha-2 agonist), phenoxybenzamine (alpha-1 blockade) in abour 3 – 4 days post-op

Carotid body tumor (Surgical pearls)

- Exposure must be liberal and adequate so that control of the vessel proximal and distal to lesion is possible
- Identify CN IX, X, XI, XII , Sympathetic chain, and protect VII before tumor is resected
- Be prepared to resect carotid and graft (have vascular surgery on stand-by)
- Be prepared for fluctuations in blood pressure during and after resection

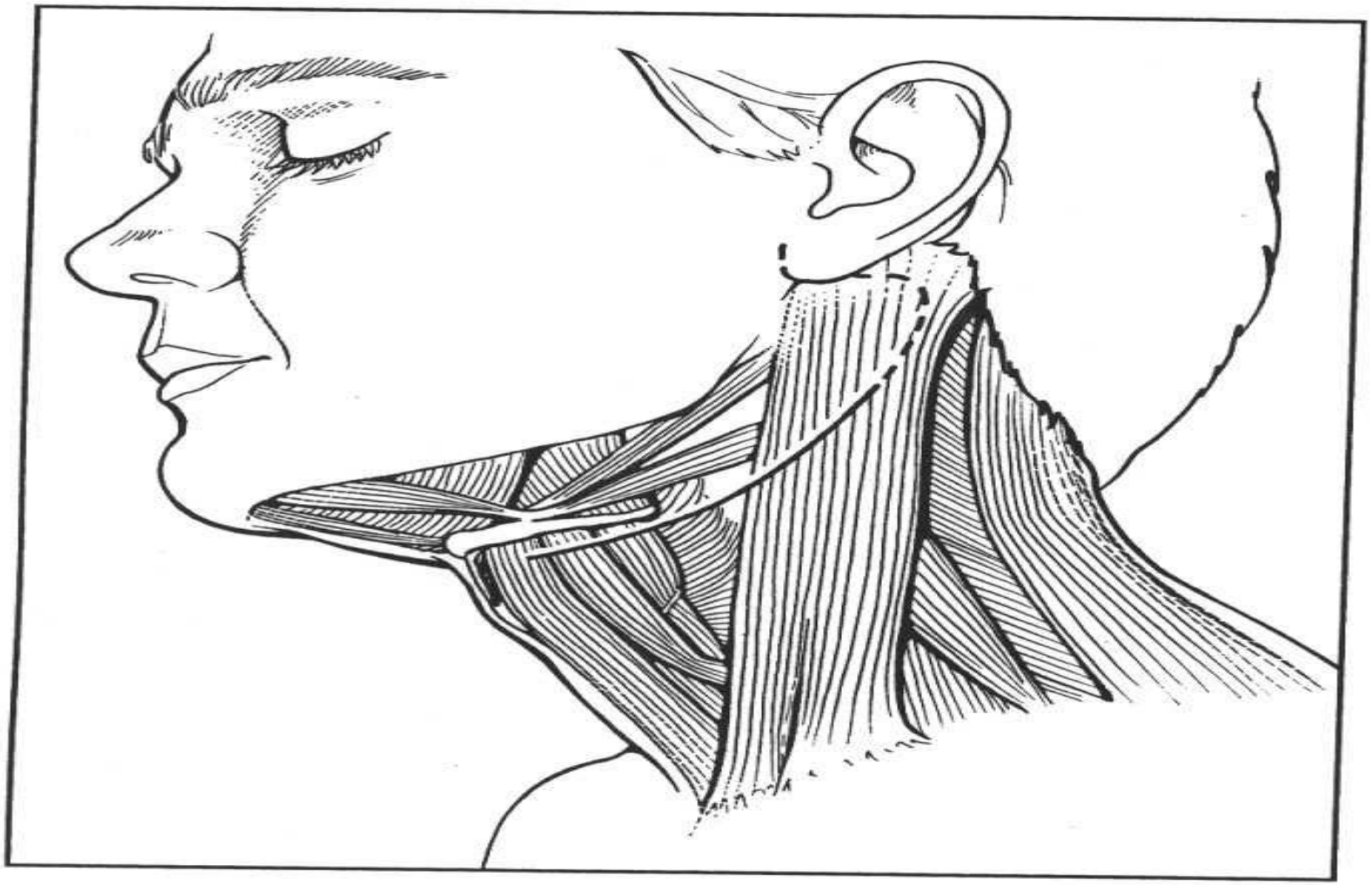


Fig. 3. With subplatysmal flap elevation, wide exposure of the carotid system can be obtained with a cosmetic skin crease incision as outlined. The preauricular extension of the incision is only needed for infratemporal extension of the tumors, or when a vagal paraganglioma is also present.

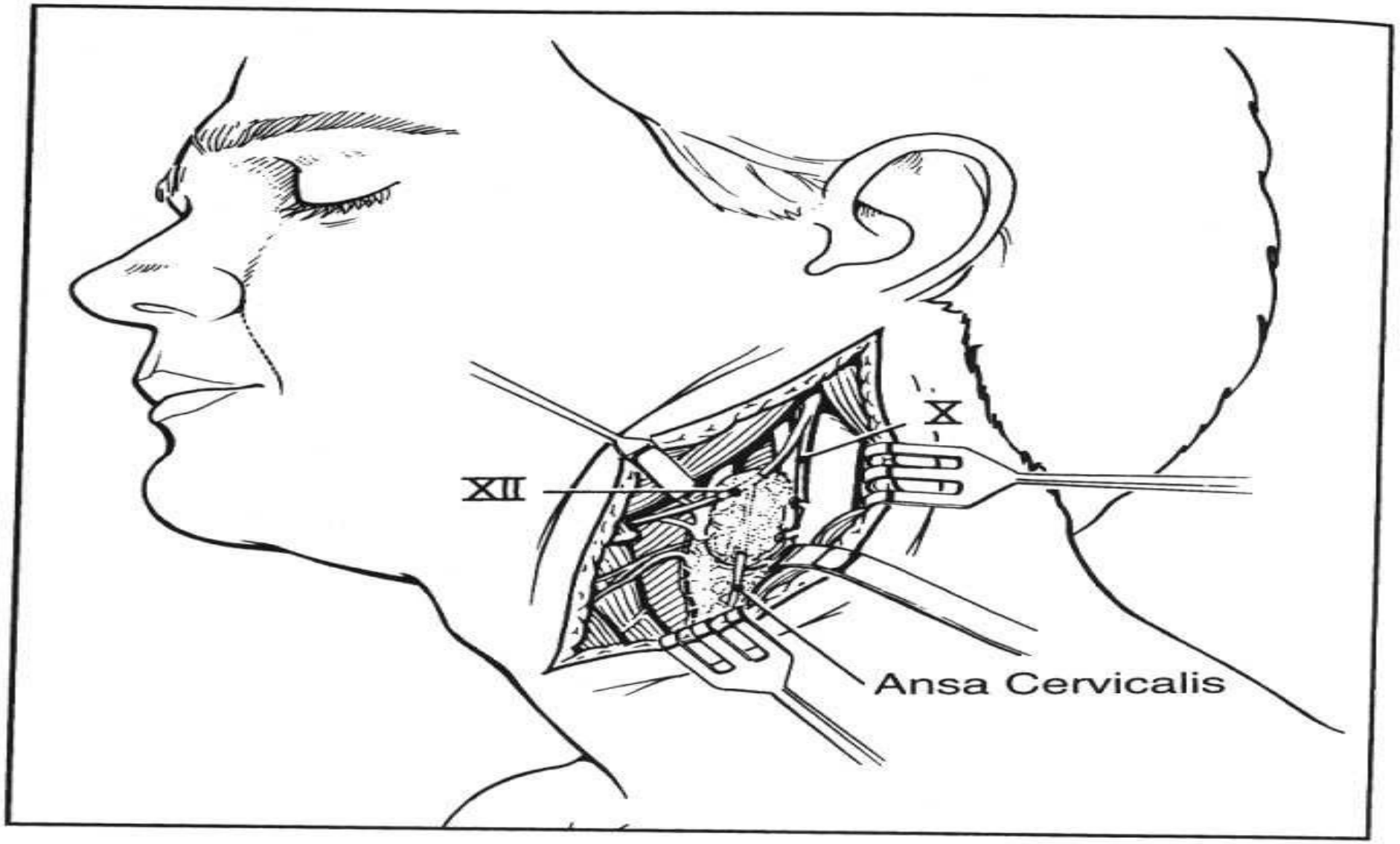


Fig. 4. With the limited selective neck finished, the hypoglossal nerve can be identified in the fascia on the lateral surface of the tumor. With division of the ansa cervicalis, cranial nerve XII can be retracted superiorly away from the tumor dissection. The fibrous union of the vagus nerve with the hypoglossal nerve is not dissected to prevent paresis of the vagus.

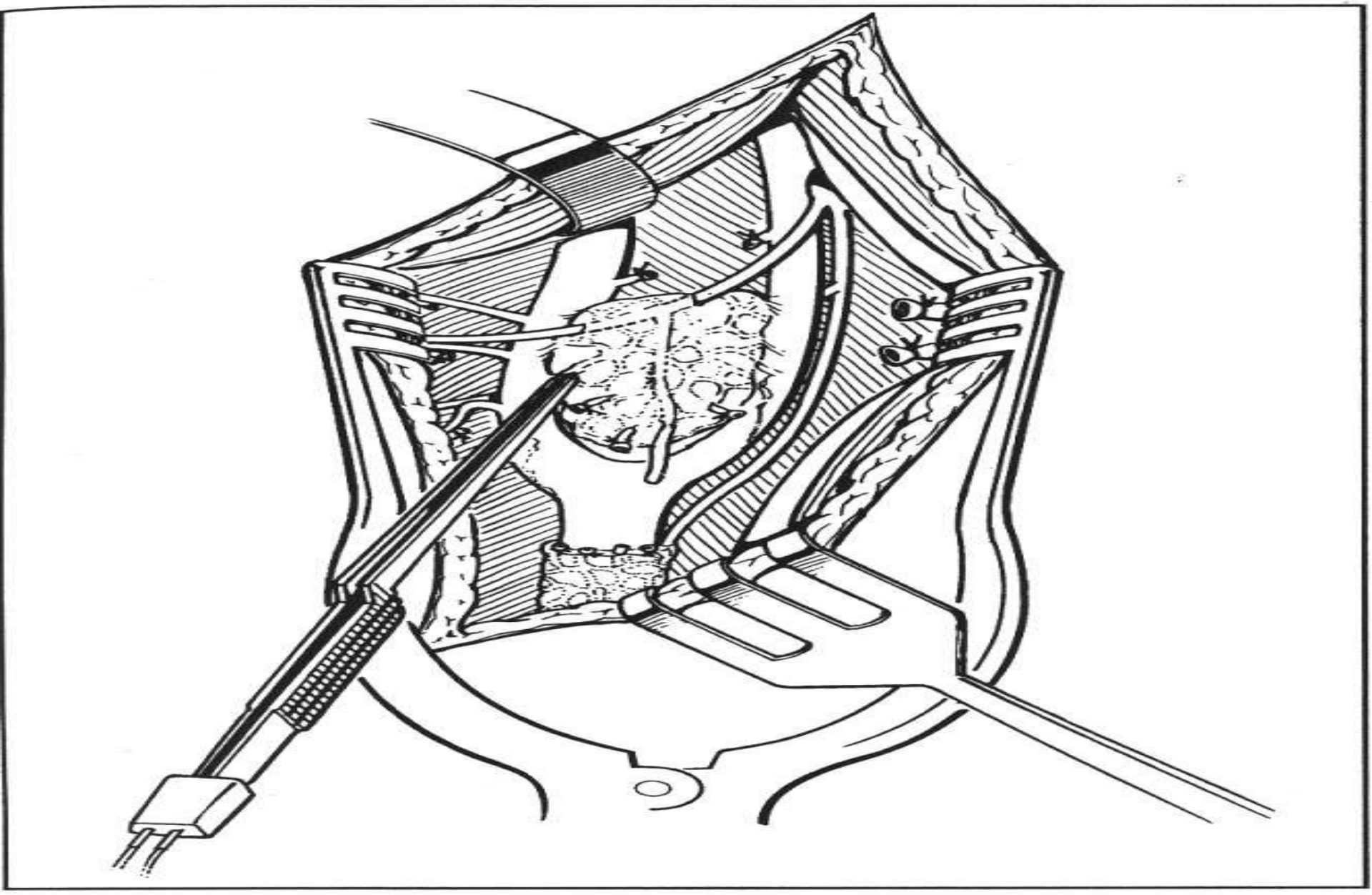


Fig. 5. The vascular envelope is divided in all directions to expose the branches of the external carotid. The use of bipolar cautery along the dissection of the carotid-tumor interface allows better visualization with much less blood in the operative field. Adjacent nerves receive less trauma with this technique.

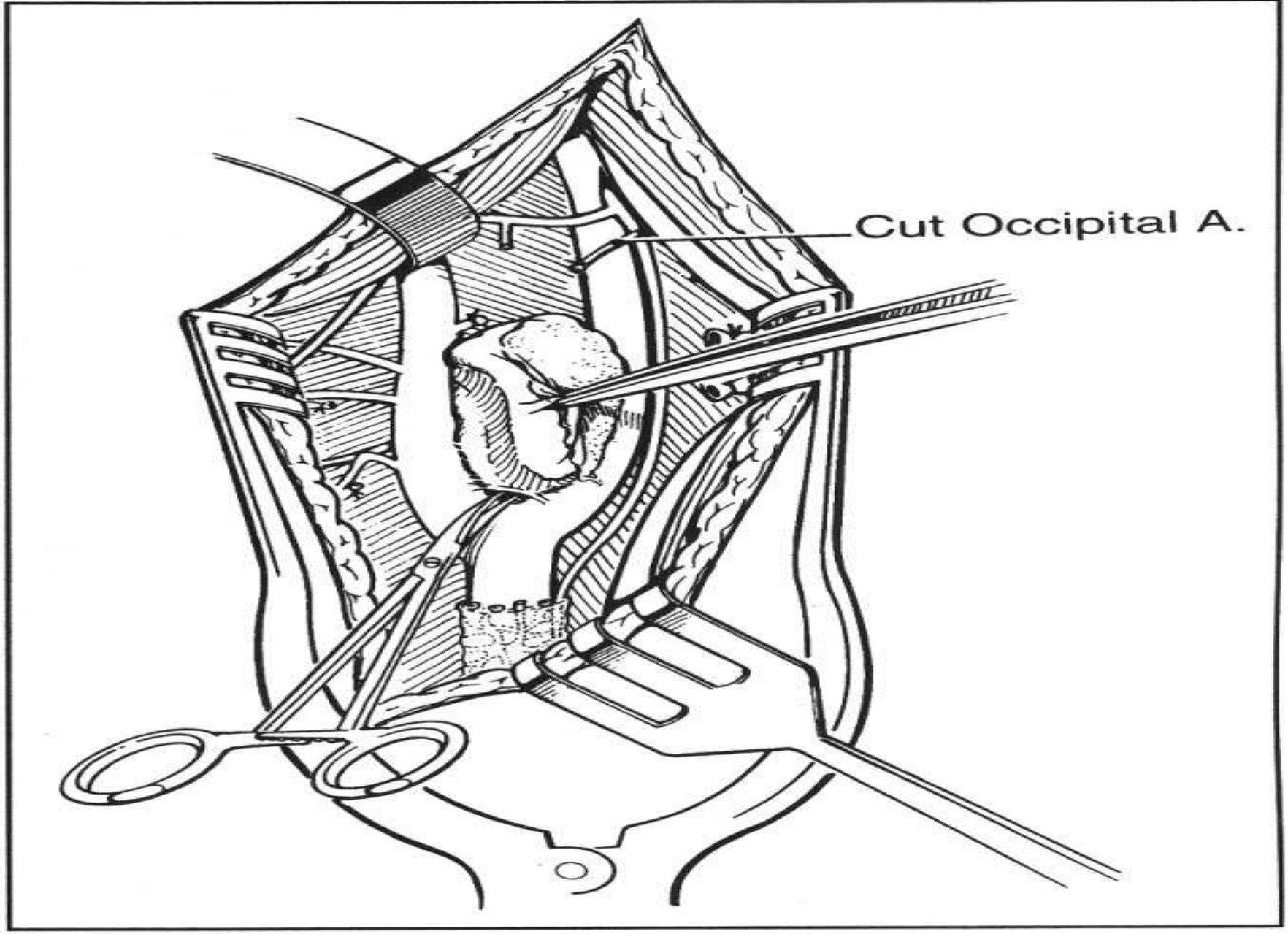


Fig. 6. With the vagus and hypoglossal nerves isolated, the tumor is dissected away from the surface of the internal carotid in a subadventitial plane if the adventitia is involved by the tumor.

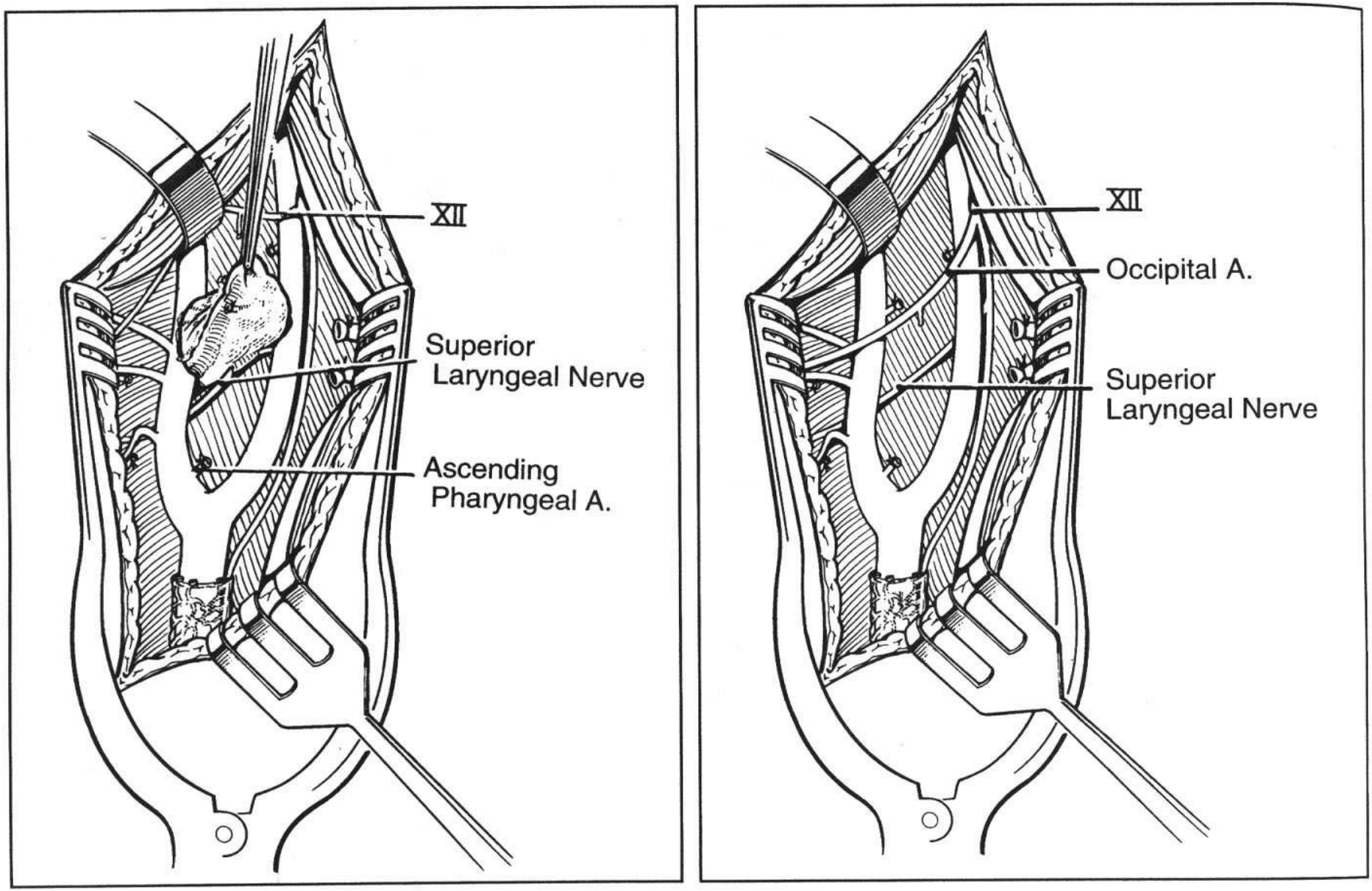


Fig. 7. **Left.** The ascending pharyngeal artery, which is identified on the deep surface of the external carotid artery just distal to the bifurcation, is ligated. The tumor freed from the bifurcation is retracted superiorly to allow dissection of the superior laryngeal nerve away from the deep surface of the tumor. **Right.** The superior laryngeal nerve can be seen deep to both the external and internal carotid arteries after the resection is complete.

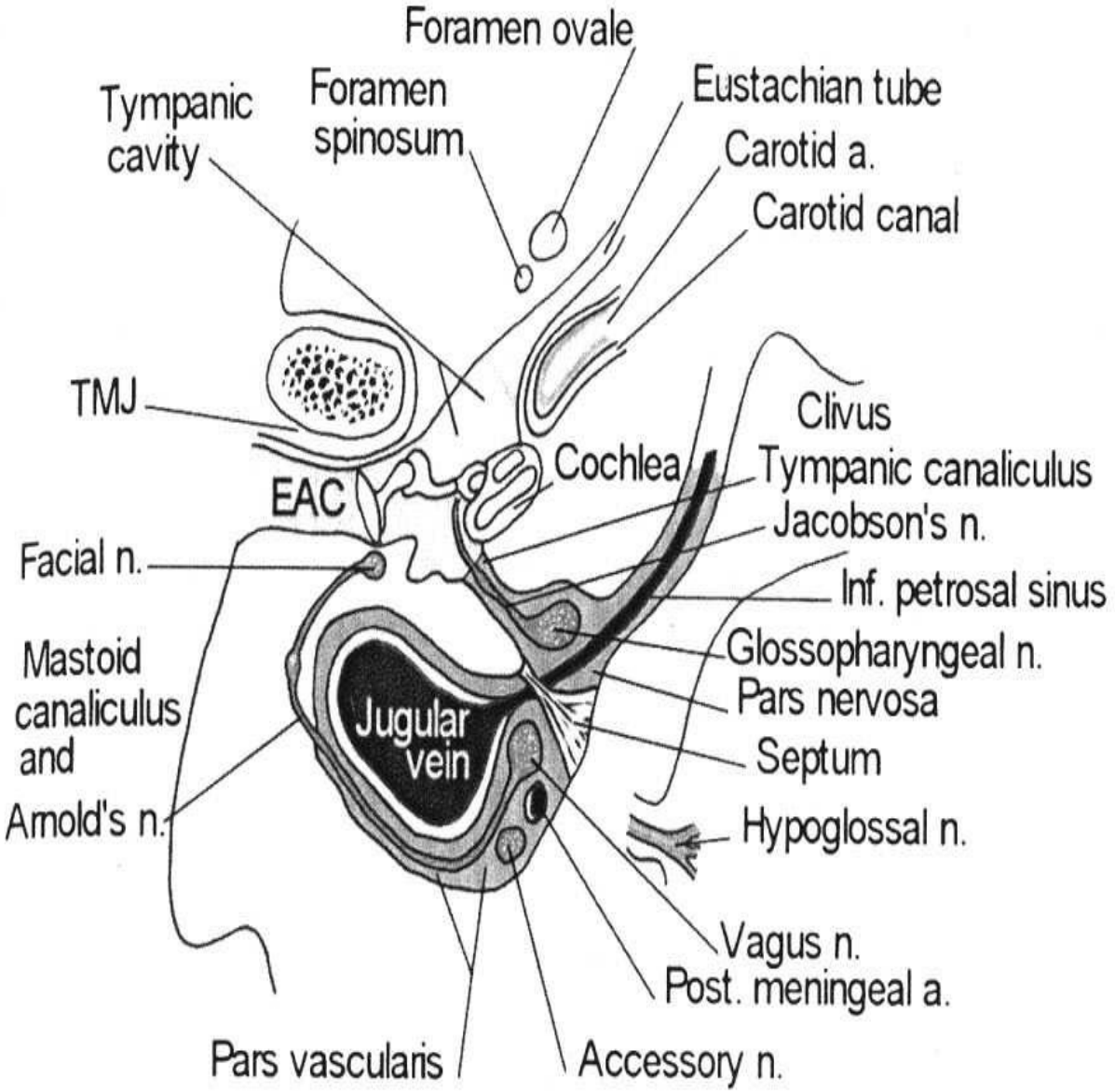


FIG. 1. Normal anatomy of the jugular fossa. Figure shows nerves and blood vessels within the jugular foramen and their relationship with the tympanic cavity and hypoglossal canal. Hemiaxial view.

Jugulotympanic Paragangliomas

- 2nd most common temporal bone tumor (after AN)
- Incidence approx 1:1,300,000
- 4:1 female to male ratio
- Median age of presentation 50-60 yrs
- No ethnic or racial predeliction
- Sporadic and familial forms (25 – 50% multicentricity)
- Functional secretion about 1-3%
- Malignancy rate < 5%
- Slow growing, spread along pathways of least resistance

Jugulotympanic Paragangliomas

- Air cell tracts most important route of spread
- Can spread outside TB via eustachian tube , vascular lumens, neurovascular foramina including IAC
- Bone erosion noted by distinct cresentric lucencies in the bone
- Hypotympanum and carotid crest separating the internal carotid from the internal jugular vein are 2 areas susceptible
- Typical course is slow continuous growth with few symptoms until advanced

Jugulotympanic Paragangliomas

- Pulsatile tinnitus
- Aural fullness
- Hearing loss (typically conductive, except if labirinth eroded)
- Cranial deficits in larger tumors, most commonly IX, X but VII, VIII, XI and XII can be affected
- Otoscopic exam reveals red or reddish-blue mass behind TM
- Brown’s sign (blanching of mass with positive pneumotoscopy)

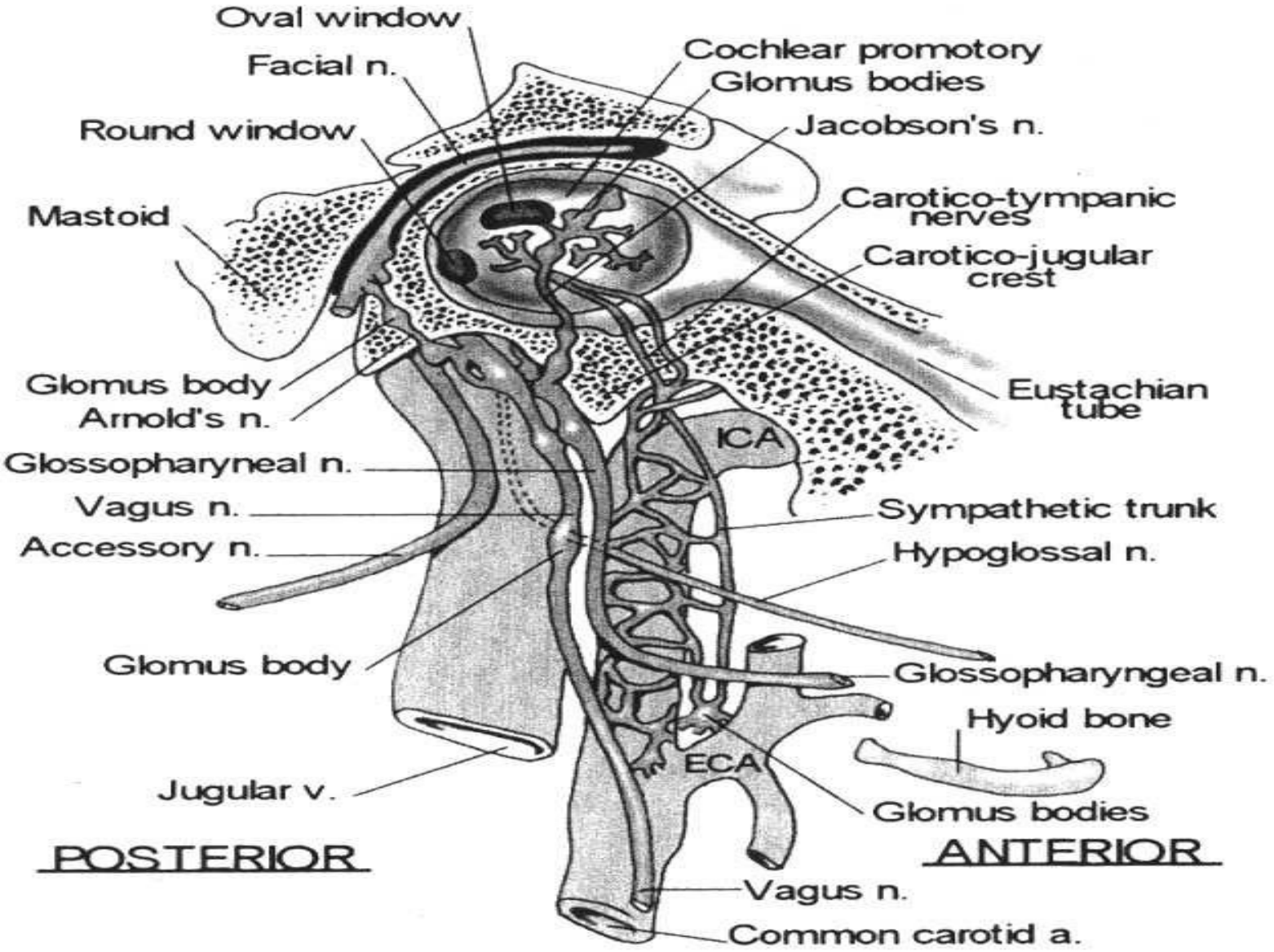


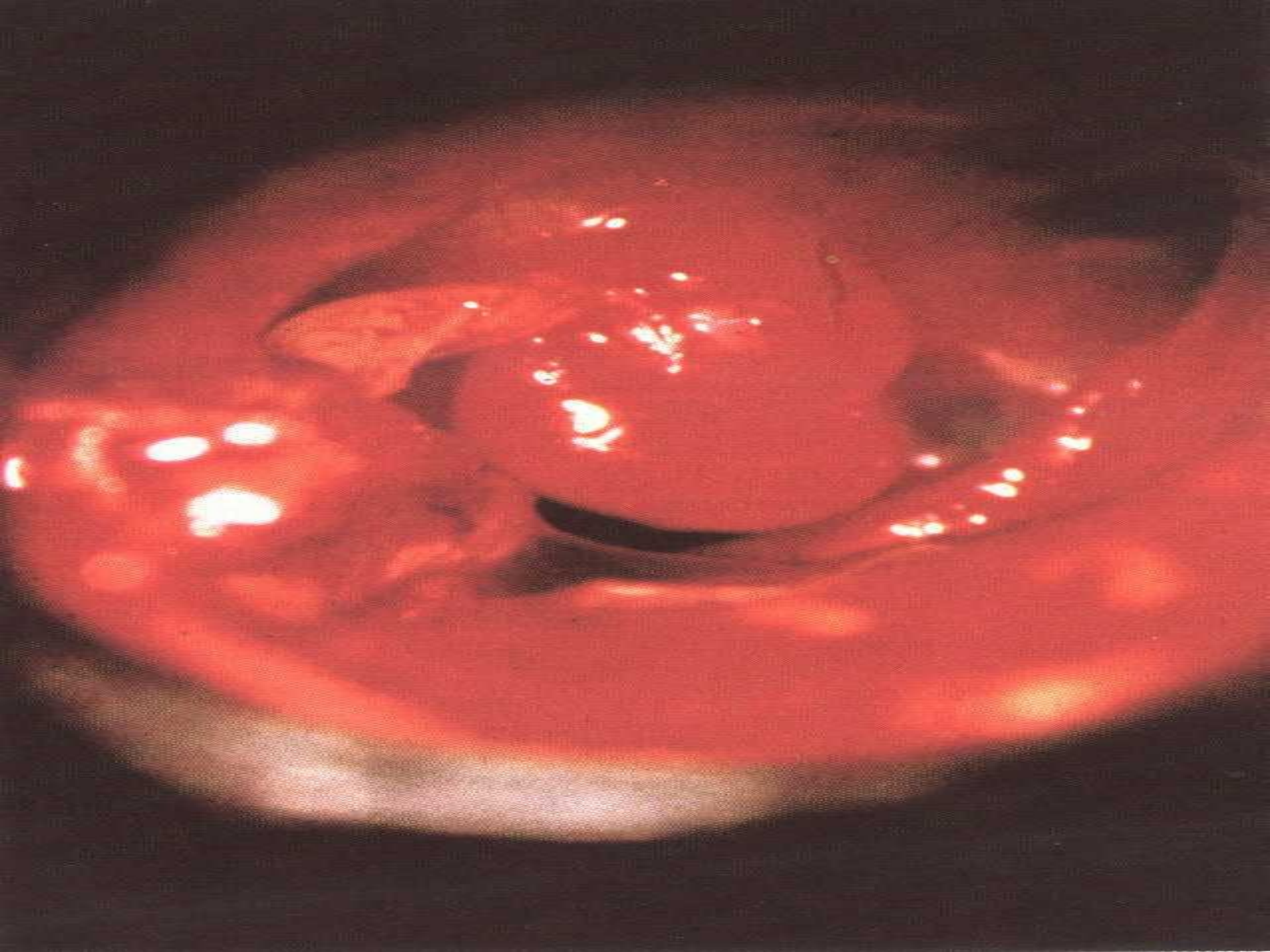
FIG. 2. Sites of glomus bodies found in the middle ear, jugular fossa, and neck. Note the relationship of glomus bodies with the cochlear promontory, Jacobson's and Arnold's nerves, and vagus nerve and common carotid artery bifurcation in the neck. View of medial wall of the middle ear cavity.

Jugulotympanic Paragangliomas

- Can occur in the adventitia of the jugular vein (glomus jugulare tumor) in 85% of cases
- Also can occur from Jacobson’s nerve, a branch of the glossopharyngeal nerve (glomus tympanicum) in 12% of cases
- Arnolds nerve , a branch of CN X, gives rise to glomus tympanicum in 3% of cases

Jugulotympanic Paragangliomas (Evaluation)

- Full audiogram with tympanometry
- Fine cut CT of Temporal bone with contrast (evaluate bone erosion, relationship to VII, cochlea and ICA)
- MRI to evaluate intracranial and intradural extension, and further define soft-tissue relationships
- 4 vessel arteriography to evaluate multicentricity, feeding vessels, embolization, BOT
- FNA not advised
- VMA, metanephrines, catecholamines
- Abdominal CT if symptomatic (flushing, HTN etc)



Glomus Tympanicum

Jugulotympanic Paragangliomas (Glasscock-Jackson Classification)

- Glomus Tympanicum
  - I. Small Mass limited to promotory
  - II. Tumor filling middle ear space
  - III. Tumor filling middle ear space and extending into mastoid
  - IV. Tumor filling middle ear, extending into the mastoid or through tympanic membrane to fill the external auditory canal; may extend anterior to carotid

Jugulotympanic Paragangliomas (Glasscock-Jackson Classification)

- Glomus Jugulare
  - I. Small tumor involving jugular bulb, middle ear, and mastoid
  - II. Tumor extending under internal auditory canal; may have intracranial extension (ICE)
  - III. Tumor extending into petrous apex; may have ICE
  - Tumor extending beyond petrous apex into clivus or infratemporal fossa; may have ICE

Fisch Classification (1981)

- Class A - Middle ear, strictly promontory
- Class B - Tympanomastoid area
- Class C - Carotid
  - C1 Carotid Foramen
  - C2 Vertical segment of carotid canal
  - C3 Horizontal segment of carotid canal
  - C4 Foramen lacerum and cavernous sinus

Fisch Classification (contd)

- Class D - Dural

- Extradural
  - De1: Intercranial Extradural extension < 2cm
  - De2: Intracranial Extradural extension > 2cm
- Intradural
  - Di1: Intracranial Intradural extension < 2cm
  - Di2: Intracranial Intradural extention > 2cm
- Arnold and Guiliam Classification not commonly used

Jugulotympanic Paragangliomas (Management)

- Decisions based on extent of tumor, and must be individualized to patient
- Considered to be more radiosensitive than carotid paragangliomas
- Goal of surgery is total or near-total excision
- Younger patients, larger tumors with CN compromise tend to be better candidates for surgery and tend to compensate better than those without pre-existing CN deficits
- Patients with secreting tumors require surgery

Jugulotympanic Paragangliomas (Management)

- Patients 65yrs and older, poor surgical candidates, and patients with multicentric tumors, XRT should be encouraged
- Always a risk of re-growth, osteoradionecrosis of temporal bone
- ORN risk is low if optimal dose of XRT of 35Gy/3wks or 45Gy/4weeks is used
- Vascular and Neurosurgical consultation encouraged prior to surgery

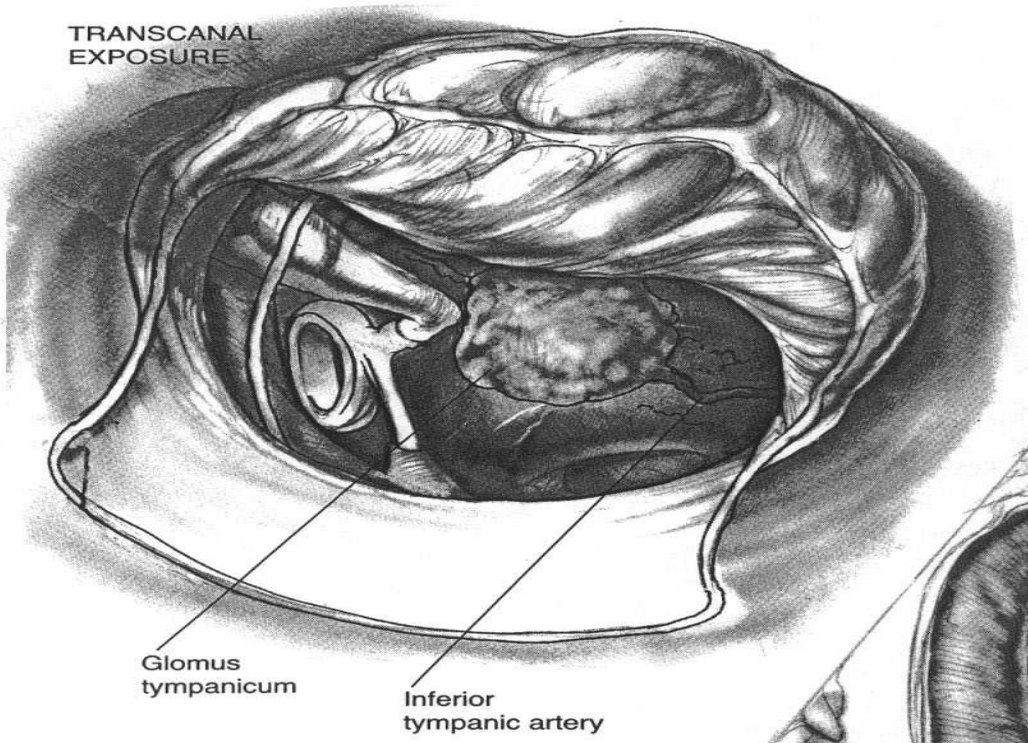
Glomus Jugulare (surgical approaches)

- Glasscock and Jackson Class I and II or Fisch C1 or C2 can be resected with extended facial recess approach
- Infratemporal fossa approach for tumors beyond petrous apex or involve cavernous sinus
- Tumors with intracranial extension may be resected with inratemporal fossa approach
- Retrosigmoid and/or suboccipital approach may be necessary for tumors with extension into posterior cranial fossa

Glomus Tympanicum (Surgical approaches)

- If limited to mesotympanum and hypotympanum, without involvement of the jugular bulb, transcanal tympanotomy may be all that is required
- Larger tumors that extend into the mastoid, a CWU mastoidectomy with extended facial recess approach used
- Larger tumors that extend beyond the middle ear or involve jugular bulb are approached like glomus jugulare tumors

FIGURE 49–1



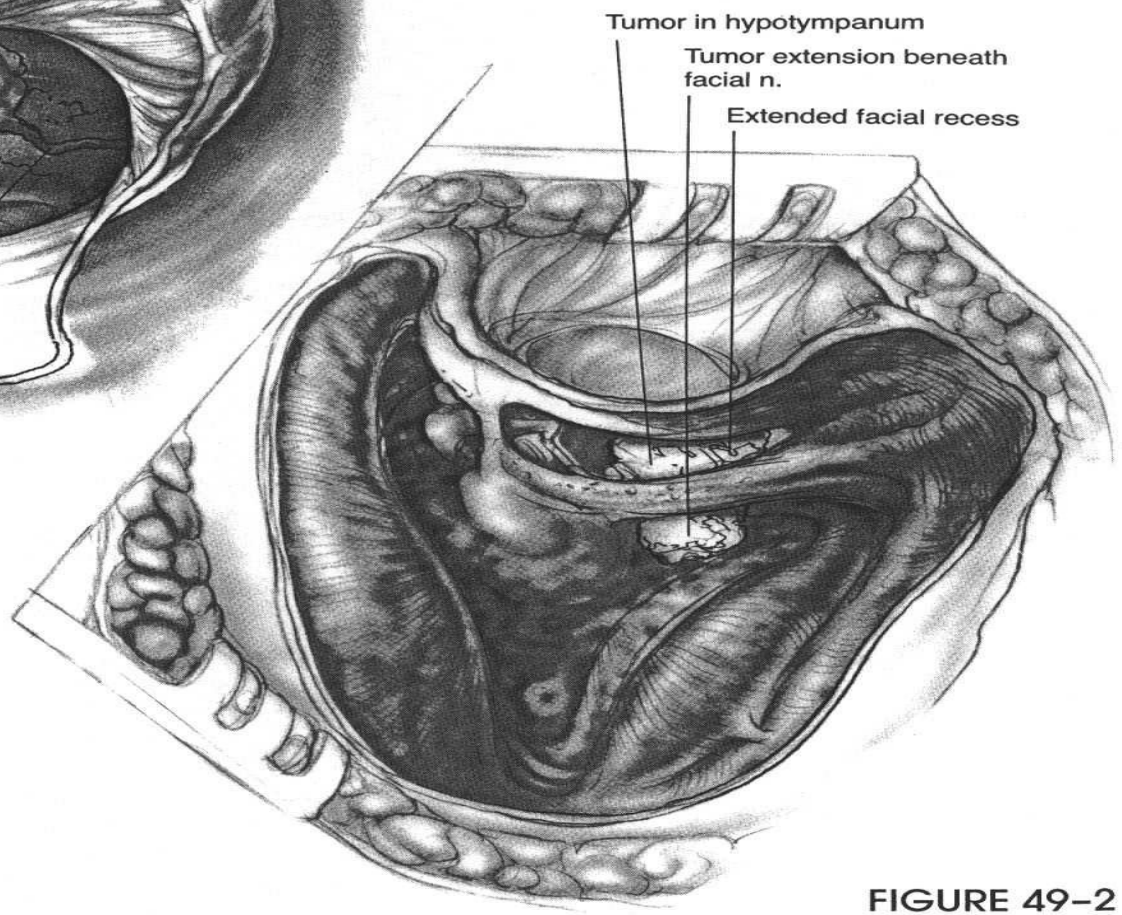


FIGURE 49–2

FIGURE 49–3

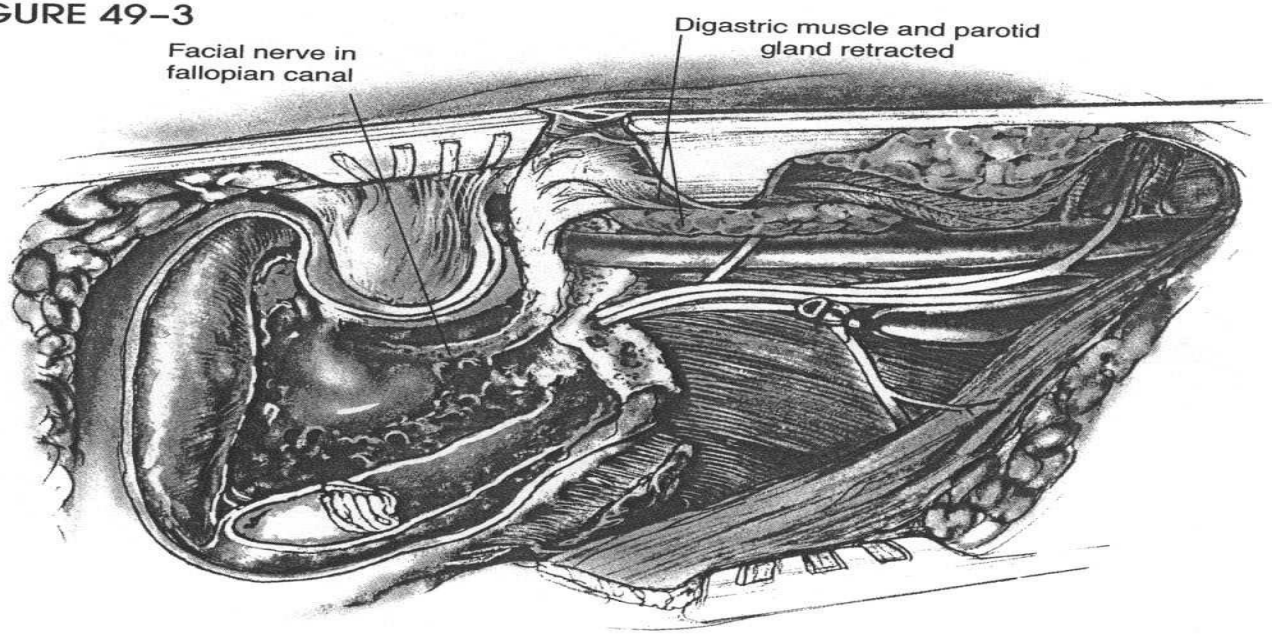


FIGURE 49–4

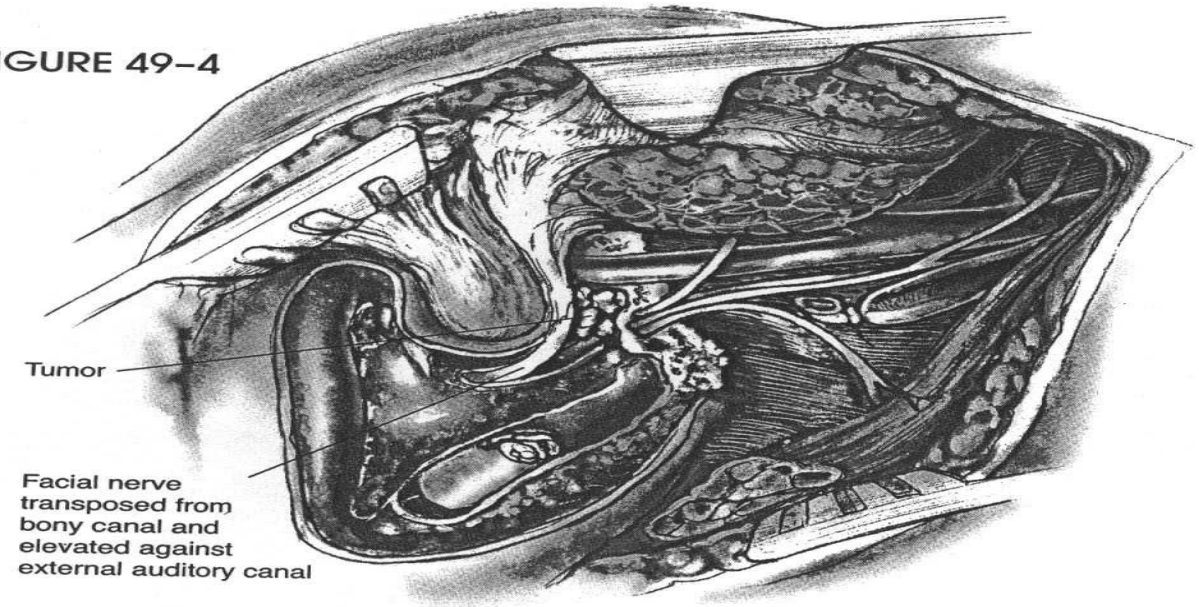
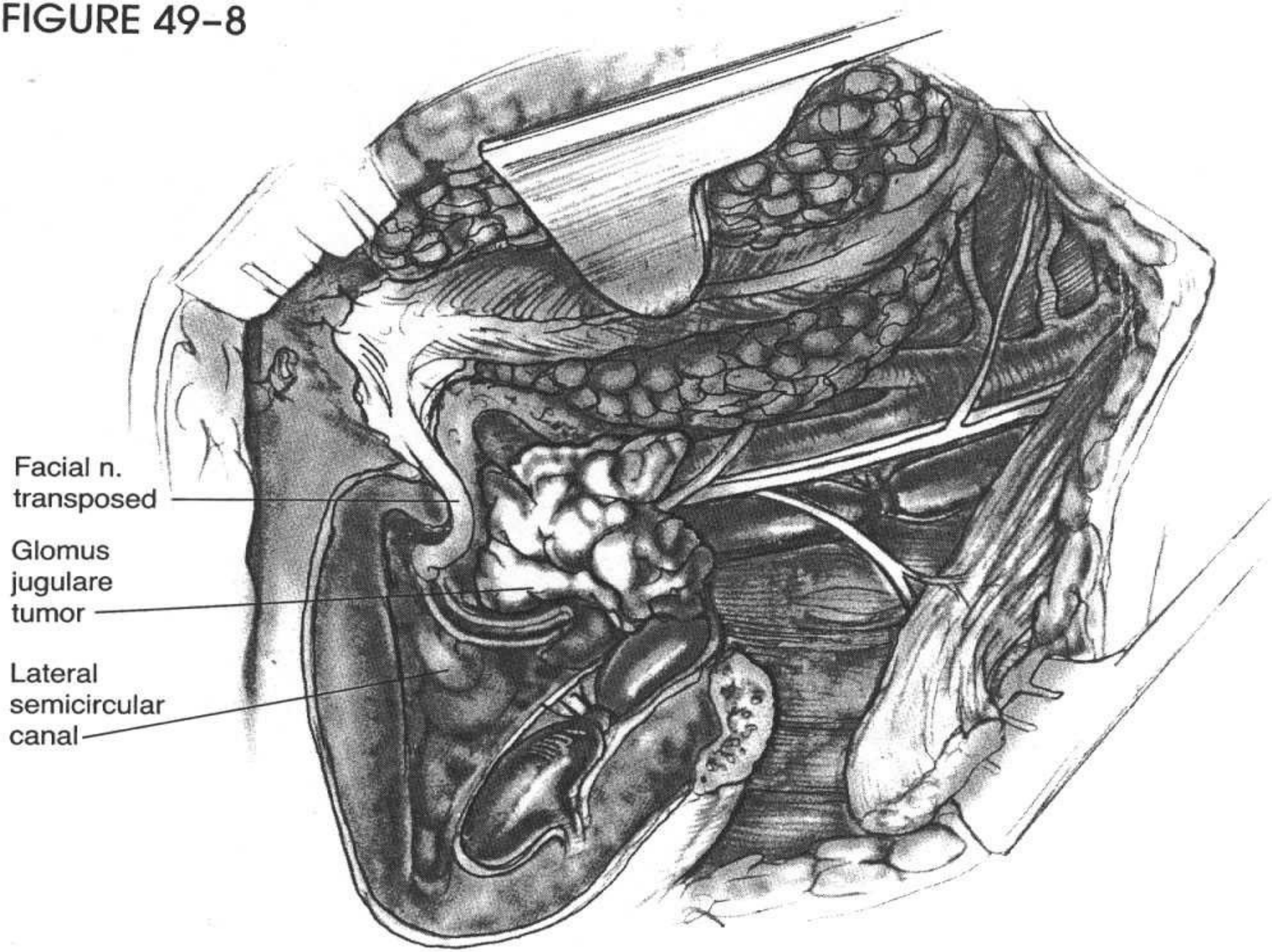


FIGURE 49–8


Facial n.
transposed
Glomus
jugulare
tumor
Lateral
semicircular
canal

Intravagal Paragangliomas

- Most commonly occur at the level of the nodose ganglion
- May occur at any point along course of vagus nerve
- Mean age of presentation is 50 yrs
- More common in females than males
- Painless mass posterior to angle of mandible
- May bulge into pharynx and cause dysphagia
- Complaints of tongue weakness, hoarseness, horner’s syndrome (Jugular foramen syndromes)
- Malignancy rate higher than others, estimated at 18%

Intravagal Paragangliomas

- Imaging studies include CT and MRI
- Angiography demonstrates tumor blush and displacement of ICA anteriorly and medially (no widening of bifurcation)
- Only one functional vagal paraganglioma reported
- Netterville reported familial occurrence as 20%
- Also noted 78% multicentricity in familial vs 23% in sporadic cases

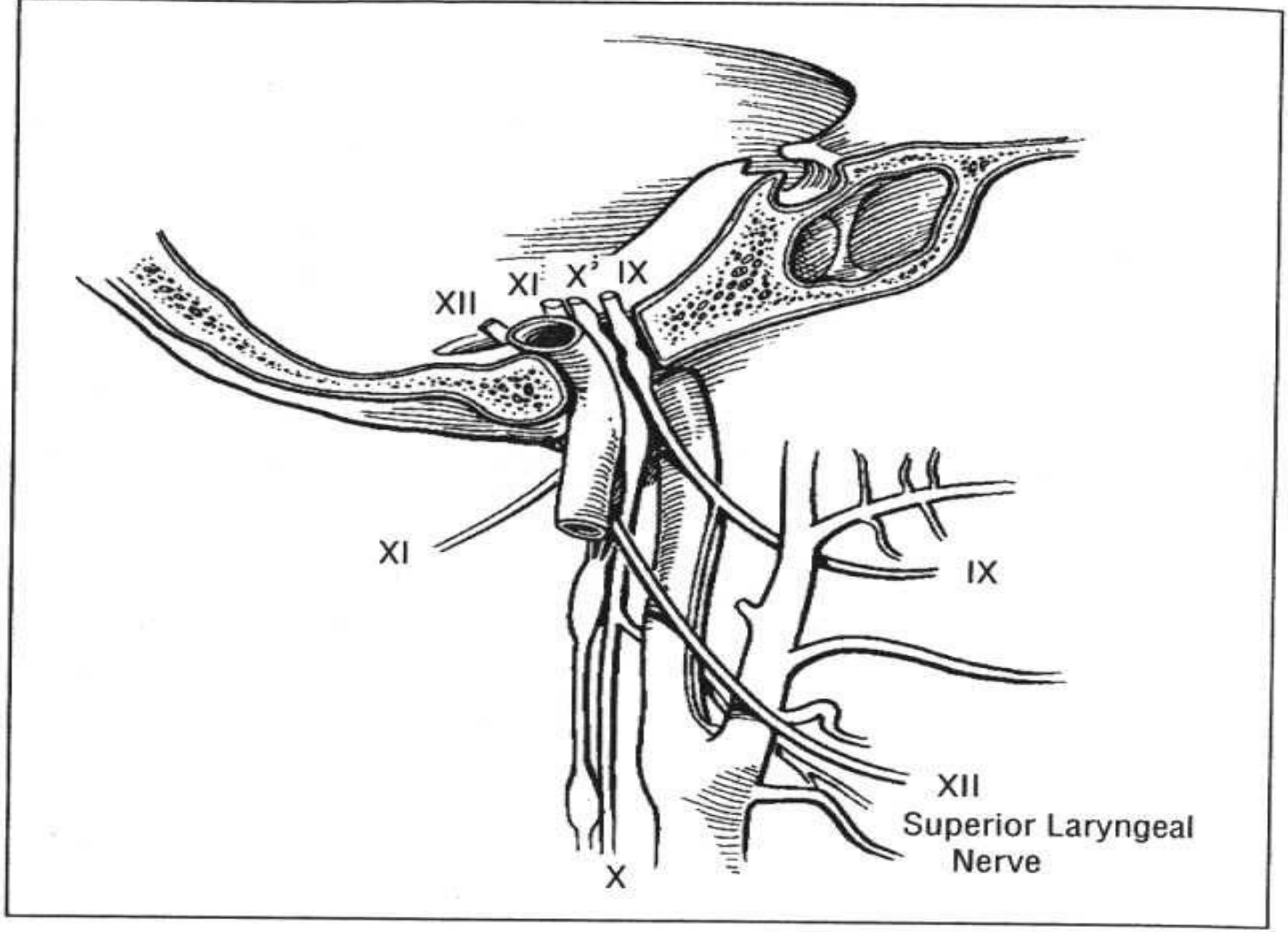


Figure 1. *Cranial nerves IX, X, XI, and XII, and the sympathetic trunk are endangered by either the growth of a vagal paraganglioma or its removal.*

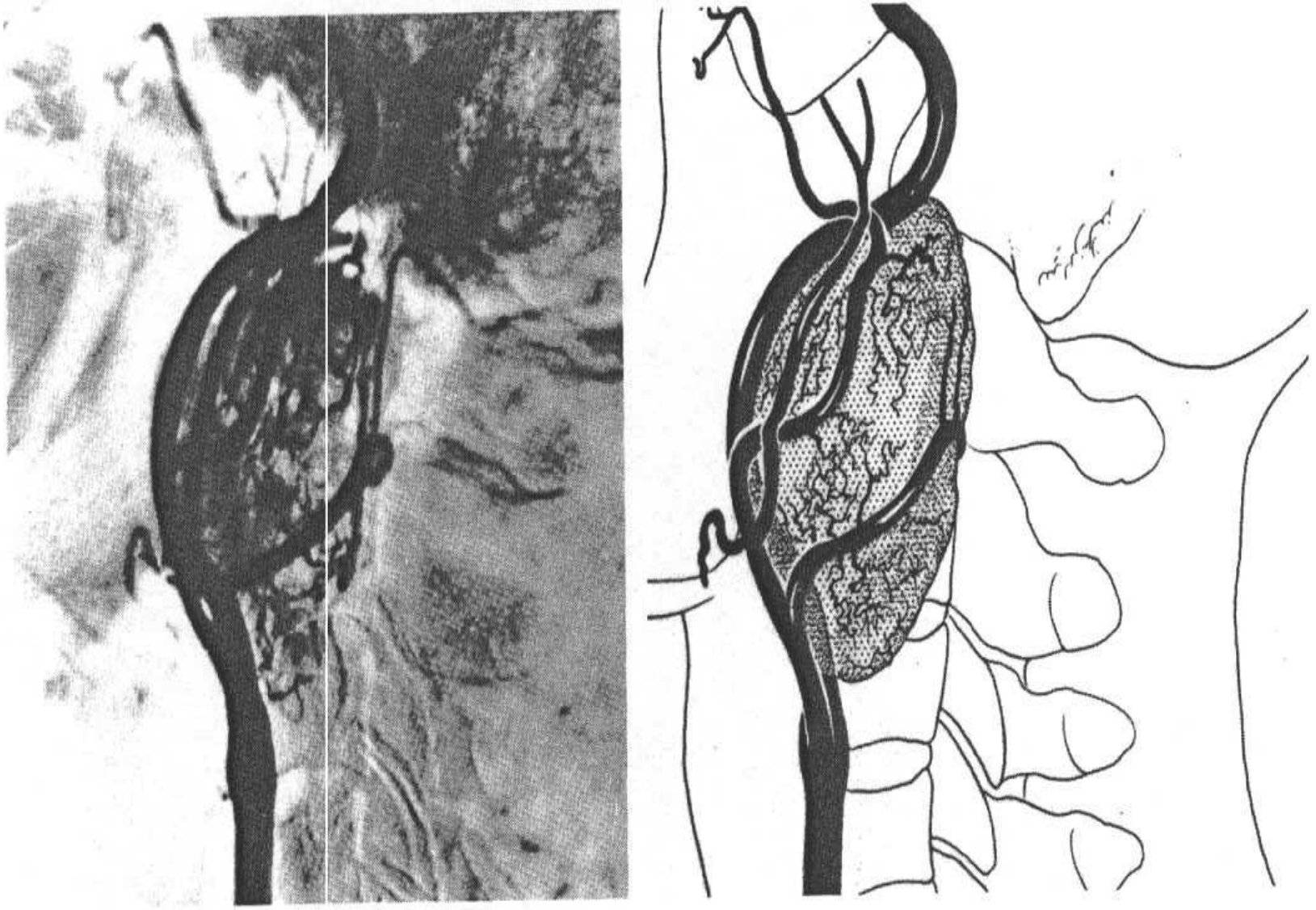


Figure 3. Left carotid angiogram in a 59 year old woman with a vagal body paraganglioma. Subtraction technique shows coarse tortuous vessels and tumor blush cephalad to bifurcation of common carotid artery. Anterior displacement of internal and external branches is depicted in drawing on right. The tumor measured 5 cm. in diameter.

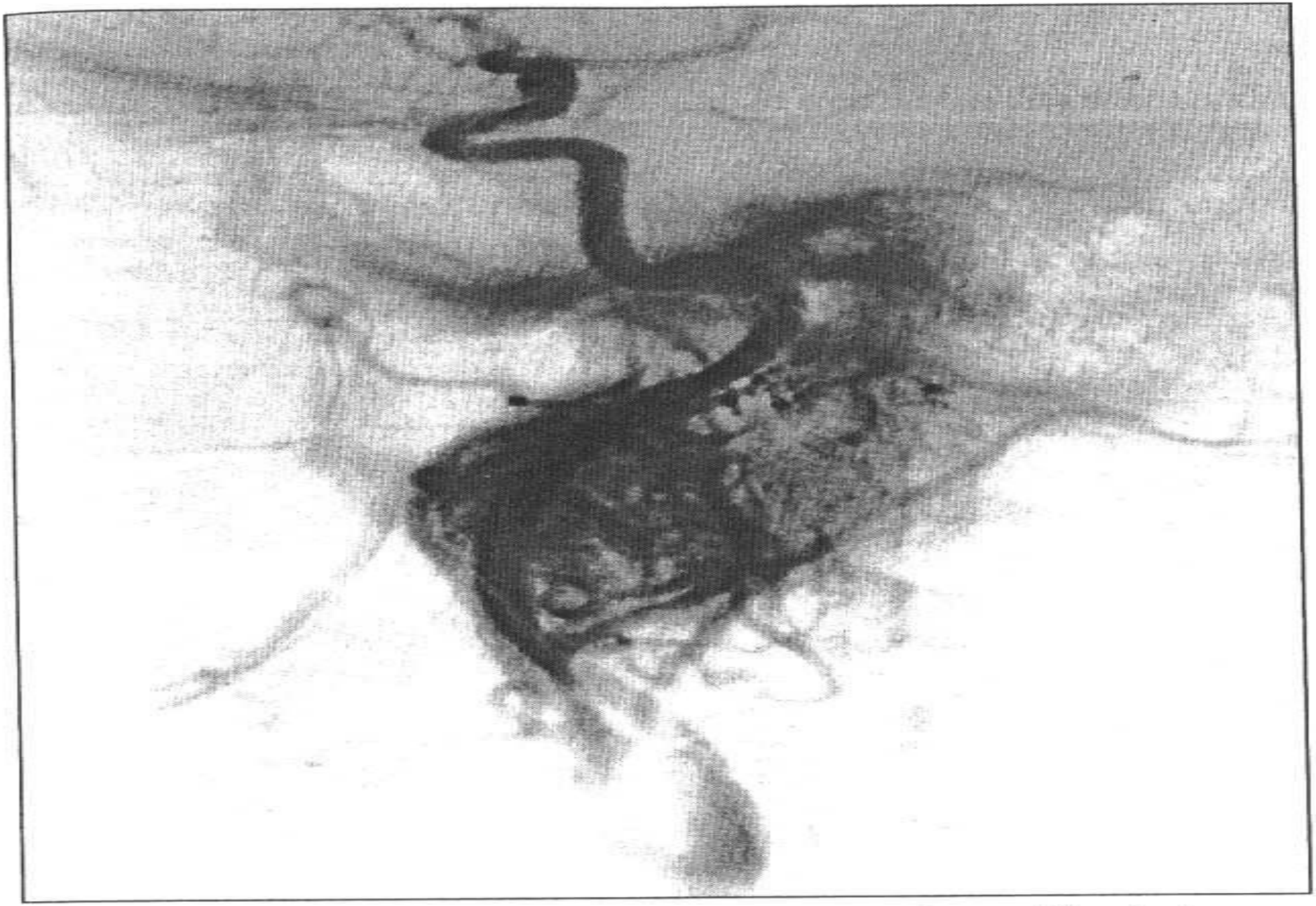


Figure 2. *Angiogram demonstrates the vascular neoplasm with anterior displacement of the internal carotid artery without widening of the carotid bifurcation.*

Intravagal Paragangliomas (Management)

- Complicated by their rarity and frequent multicentricity/bilaterallity
- Controversial as to best therapy
- Surgery proponents offer this choice as best possibility for complete removal
- XRT proponents site morbidity from surgery as prohibitive
- XRT has not been shown to be curative, and has risk of ORN of temporal bone
- Surgery resection by transcervical approach, combined with lateral skull base approach depending on extent

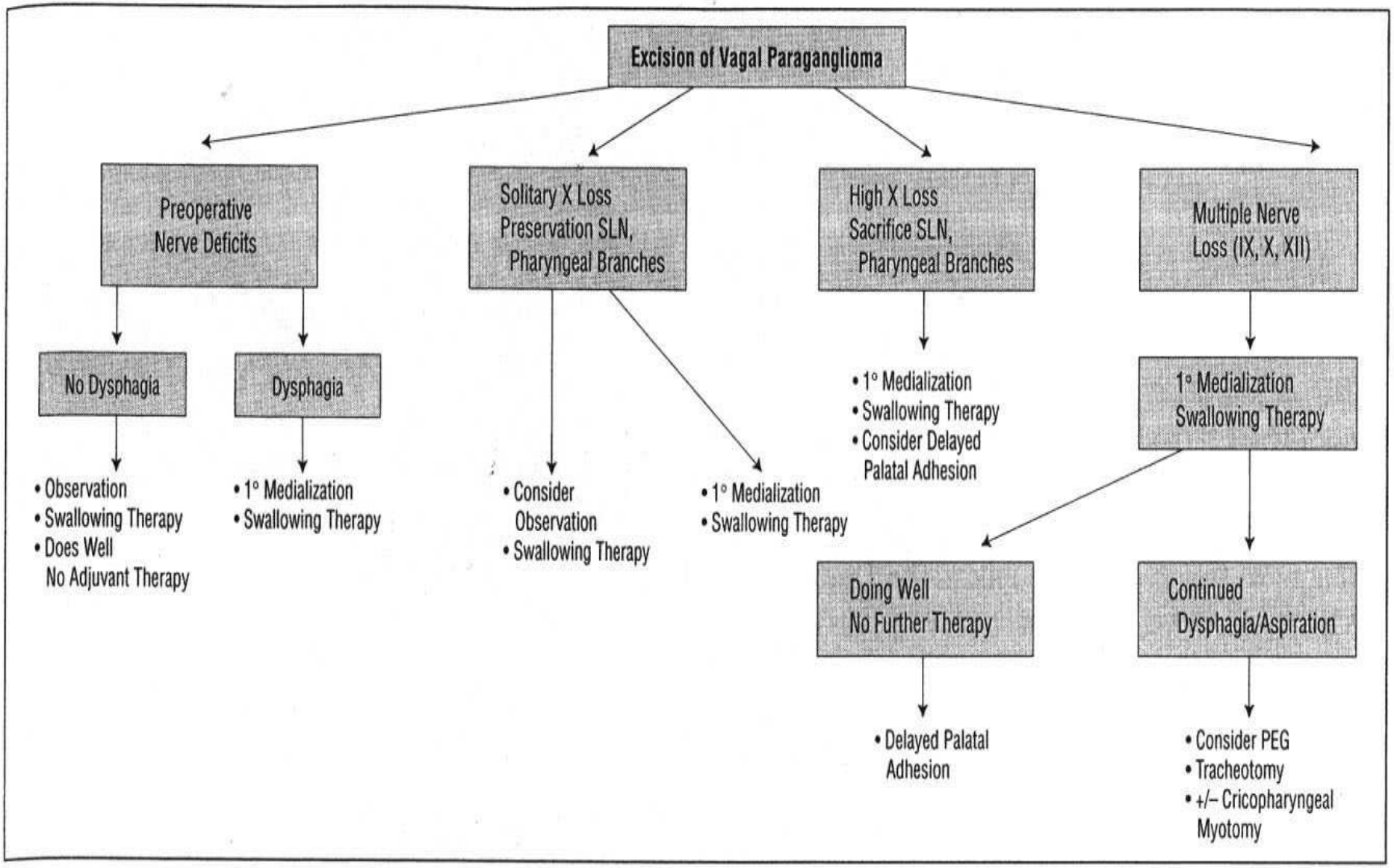


Figure 5. *Algorithim for the management of lower cranial nerve deficits following the excision of a vagal paraganglioma. 1° medialization indicates Silastic medialization laryngoplasty done at the time of surgery; SLN, superior laryngeal nerve; PEG, percutaneous endoscopic gastrostomy; IX, glossopharyngeal nerve; X, vagus nerve; and XII, hypoglossal nerve.*

Summary and Conclusions

- Paragangliomas are relatively rare, slow growing and generally benign tumors which, due to their location and growth characteristics, can inflict severe morbidity on the afflicted patient
- Surgical management is generally the mainstay for treatment, though XRT is also used in select cases
- New frontiers in screening and imaging have significantly improved overall survival and morbidity
- Several controversies exist regarding the best therapy

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